Ozanimod induction and maintenance treatment for ulcerative colitis

TOUCHSTONE Study Group

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ORIGINAL ARTICLE

Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis

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ABSTRACT

BACKGROUND

Ozanimod (RPC1063) is an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5 that induces peripheral lymphocyte sequestration, potentially decreasing the number of activated lymphocytes circulating to the gastrointestinal tract.

METHODS

We conducted a double-blind, placebo-controlled phase 2 trial of ozanimod in 197 adults with moderate-to-severe ulcerative colitis. Patients were randomly assigned, in a 1:1:1 ratio, to receive ozanimod at a dose of 0.5 mg or 1 mg or placebo daily for up to 32 weeks. The Mayo Clinic score was used to measure disease activity on a scale from 0 to 12, with higher scores indicating more severe disease; subscores range from 0 to 3, with higher scores indicating more severe disease. The primary outcome was clinical remission (Mayo Clinic score ≤2, with no subscore >1) at 8 weeks.

RESULTS

The primary outcome occurred in 16% of the patients who received 1 mg of ozanimod and in 14% of those who received 0.5 mg of ozanimod, as compared with 6% of those who received placebo (P=0.048 and P=0.14, respectively, for the comparison of the two doses of ozanimod with placebo). Differences in the primary outcome between the group that received 0.5 mg of ozanimod and the placebo group were not significant; therefore, the hierarchical testing plan deemed the analyses of secondary outcomes exploratory. Clinical response (decrease in Mayo Clinic score of ≥3 points and ≥30% and decrease in rectal-bleeding subscore of ≥1 point or a subscore ≤1) at 8 weeks occurred in 57% of those receiving 1 mg of ozanimod and 54% of those receiving 0.5 mg, as compared with 37% of those receiving placebo. At week 32, the rate of clinical remission was 21% in the group that received 1 mg of ozanimod, 26% in the group that received 0.5 mg of ozanimod, and 6% in the group that received placebo; the rate of clinical response was 51%, 35%, and 20%, respectively. At week 8, absolute lymphocyte counts declined 49% from baseline in the group that received 1 mg of ozanimod and 32% from baseline in the group that received 0.5 mg. The most common adverse events overall were anemia and headache.

CONCLUSIONS

In this preliminary trial, ozanimod at a daily dose of 1 mg resulted in a slightly higher rate of clinical remission of ulcerative colitis than placebo. The trial was not large enough or of sufficiently long duration to establish clinical efficacy or assess safety. (Funded by Receptos; TOUCHSTONE ClinicalTrials.gov number, NCT01647516.)

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Ulcerative colitis is a chronic immune-mediated disease of the colon that is currently treated with mesalamine, glucocorticoids, thiopurines, and biologic agents.[1,2] A lack of universal response, the risks of infection and neoplasia, a requirement for parenteral administration, and the development of antidrug antibodies have created a need for safe and effective oral therapies.

The sphingosine-1-phosphate (S1P) subtype 1 (S1P1) receptor is a member of a family of five widely expressed receptors (S1P1 through S1P5) that are responsible for regulating multiple immunologic and cardiovascular effects.[3,4] Cell-surface–associated S1P1 receptor plays a crucial role in the trafficking of lymphocytes from lymphoid organs.[5,6] S1P1-receptor agonists induce internalization and degradation of the S1P1 receptor, rendering B and T lymphocytes incapable of migrating from secondary lymphoid organs, which leads to a reversible reduction in circulating lymphocytes in the blood.[4,5,7]

Patients treated with fingolimod (Gilenya, Novartis), a S1P-receptor modulator that has been approved for the treatment of relapsing multiple sclerosis,[8,9] have a decrease from baseline of 70 to 80% in the peripheral-blood lymphocyte count owing to lymph-node sequestration of naive and central memory lymphocytes. In contrast, the number of effector memory T cells remains comparatively unchanged, which probably preserves immunosurveillance.[10,11] However, rare cases of serious disseminated varicella–zoster and herpes simplex infections have been reported.[12] Fingolimod is not selective for the S1P1 receptor and binds to an additional three of the five receptor subtypes (S1P3, S1P4, and S1P5), which may lead to adverse events, including cardiovascular effects such as bradycardia (in <1% of patients), second-degree atrioventricular blocks (in 4%), elevation of liver aminotransferase levels (in 14%), and macular edema (in <1%).[13-15]

Ozanimod (RPC1063) is a new oral S1P1-receptor and S1P5-receptor modulator with no activity on S1P2, S1P3, and S1P4.[16] A phase 2 trial of ozanimod in patients with relapsing multiple sclerosis showed a dose-dependent reduction in circulating lymphocytes that was associated with significant reductions in inflammatory and neurodegenerative brain lesions, with minimal effects on heart rate and liver enzymes.[17] We evaluated the efficacy and safety of ozanimod in patients with moderately to severely active ulcerative colitis.

METHODS

TRIAL OVERSIGHT

From December 2012 through April 2015, we conducted this randomized, double-blind, placebo-controlled phase 2 trial of induction and maintenance therapy at 57 centers in 13 countries. The protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board at each center. All the patients provided written informed consent.

The members of the steering committee (see the Supplementary Appendix, available at NEJM.org) designed the trial in collaboration with the sponsor (Receptos). Data were collected by a contract research organization (Pharmaceutical Product Development) and analyzed by the sponsor. The sponsor and the steering committee interpreted the data jointly. All the authors had full access to the data. The first two authors wrote the first draft of the manuscript, and all the authors contributed to subsequent drafts, made a collective decision to submit the manuscript for publication, and vouch for the completeness and veracity of the data and analyses reported and for the adherence of the trial to the protocol. Editorial support was provided by the sponsor and by Robarts Clinical Trials (funded by the sponsor). Confidentiality agreements were in place between the sponsor and all the authors.

PATIENTS

Eligible patients were 18 to 75 years of age and had ulcerative colitis, with a Mayo Clinic score[18] of 6 to 12 and an endoscopic subscore of 2 or 3, as determined by blinded central read. The Mayo Clinic score was used to measure disease activity on a scale from 0 to 12, with higher values indicating more severe disease[18]; subscores range from 0 to 3, with higher scores indicating more severe disease. Treatment with oral aminosalicylates or prednisone (≤30 mg per day) was required to be at stable doses. Patients receiving biologic agents or azathioprine, mercaptopurine, or methotrexate were required to discontinue these agents 5 half-lives before starting the trial regimen and 4 weeks before their screening endoscopy, respectively. A documented presence of varicella–zoster virus IgG antibody or complete varicella–zoster vaccination was required in order

to minimize the risk of infection. Additional eligibility criteria and the exclusion criteria are provided in the Supplementary Appendix.

TRIAL DESIGN

The trial included blinded induction and maintenance periods and an optional open-label period (Fig. S1 in the Supplementary Appendix); this article describes the induction and maintenance periods. Patients were randomly assigned, in a 1:1:1 ratio, to receive oral ozanimod at a dose of 0.5 mg or 1 mg (the choice of these doses was based on modeling of preclinical and phase 1 data) or placebo, once daily. Patients underwent dose escalation during the first week after randomization; thereafter, the patients received the randomly assigned dose for 8 weeks (see the Supplementary Appendix). Randomization was performed centrally with the use of a computerized system and was stratified according to previous exposure to a tumor necrosis factor (TNF) antagonist (yes or no). Glucocorticoid doses were maintained unchanged through week 8, after which time the doses could be tapered at the discretion of the investigator. Patients with clinical response at week 8 continued their blinded regimen during the maintenance period. Patients who did not have a response at week 8 were allowed to cross over to optional open-label treatment.

Patients were assessed on day 1 (baseline), at weeks 4 and 8 (during the induction period), and at weeks 20 and 32 (during the maintenance period). Flexible sigmoidoscopy with colonic biopsy was performed at screening and at weeks 8 and 32. Blinded central reading of endoscopic videos and histologic findings was performed. Adverse events and use of concomitant medications were recorded through 32 weeks. Additional monitoring for adverse events that were considered to be potentially relevant to S1P-receptor modulation is described in the Supplementary Appendix. Blood samples were obtained at each visit for clinical chemical and hematologic studies and for the measurement of the C-reactive protein concentration. Stool samples were obtained at baseline and at weeks 8 and 32 for the measurement of fecal calprotectin and lactoferrin concentrations.

The primary outcome was clinical remission (Mayo Clinic score ≤2, with no subscore >1)[19,20] at week 8. The comparison of 1 mg of ozanimod with placebo was hierarchically ranked before the comparison of 0.5 mg of ozanimod with placebo. Hierarchically ranked secondary outcomes at week 8 were clinical response (reduction in the Mayo Clinic score of ≥3 points and ≥30% from baseline, with a decrease in the rectal-bleeding subscore of ≥1 point or a subscore of ≤1[19,20]), change from baseline in the Mayo Clinic score, and mucosal healing (endoscopy subscore ≤1[19,20]). Exploratory outcomes included clinical response, clinical remission, mucosal healing, and change in the Mayo Clinic score at week 32 and histologic remission (Geboes score <2, on a scale from 0 to 5, with higher scores indicating more severe histologic inflammation)[21] at weeks 8 and 32. We also examined changes from baseline in the absolute lymphocyte count and the concentrations of C-reactive protein, calprotectin, and lactoferrin.

STATISTICAL ANALYSIS

Demographic characteristics and disease characteristics at baseline were compared with the use of descriptive statistics. Proportions of patients with clinical remission at week 8 were compared with the use of the Cochran–Mantel–Haenszel chi-square test, stratified according to status with respect to previous receipt of TNF-antagonist therapy. Rates of clinical remission at week 32 and clinical response and mucosal healing at weeks 8 and 32 were analyzed similarly. The changes in the Mayo Clinic score from baseline to week 8 and to week 32 were analyzed with the use of analysis of covariance models with treatment group, status with respect to previous TNF-antagonist therapy, and baseline value of the corresponding outcome included as covariates. Nonparametric methods were used for analysis of the changes from baseline in the absolute lymphocyte count and the concentrations of C-reactive protein, calprotectin, and lactoferrin.

To control for multiple comparisons, a closed hierarchical procedure was used for the primary and secondary outcomes. The order of testing was the primary-outcome comparison of remission rates at week 8 in the group that received 1 mg of ozanimod with the placebo group, followed by the comparison of remission rates at week 8 in the group that received 0.5 mg of ozanimod with the placebo group if the result of the primary analysis was significant (two-sided $P<0.05$), followed by each major secondary

outcome in order (clinical response, change in Mayo Clinic score from baseline, and mucosal healing), with comparisons for the 1-mg dose preceding those for the 0.5-mg dose. Analyses of outcomes at week 32 were prespecified as other secondary outcomes and were considered to be exploratory. The plan specified that formal testing would stop if the results were not significant, and all subsequent analyses would be considered to be exploratory and the corresponding P values nominal.

Efficacy analyses were performed according to the intention-to-treat principle. For the primary analysis, as well as for the analyses of all secondary outcomes that were defined as proportions, patients who had missing data were classified as not having had a response. Patients who did not proceed to the maintenance period were considered not to have had a response at week 32. For the secondary outcome of change in the Mayo Clinic score from baseline, as well as for the analyses of change from baseline in the concentrations of C-reactive protein, calprotectin, and lactoferrin, missing values were replaced by the last observation carried forward.

To compare the consistency of the effect of the regimen on clinical remission with placebo and with ozanimod at a dose of 0.5 mg or 1 mg once daily, we performed prespecified subgroup analyses (in subgroups defined according to previous use of TNF antagonists [yes or no], age [<median or ≥median], sex, colonic area involved [left side or extensive], and baseline Mayo Clinic score [≤8 or >8]). Multiple post hoc subgroup analyses were also performed (see the Supplementary Appendix).

We anticipated that 10% of the patients in the placebo group would have clinical remission after induction therapy. We calculated that enrollment of 180 patients (60 patients per group) would provide the trial with 80% power to detect an absolute difference of 21 percentage points in the rate of clinical remission at week 8 between the placebo group and each ozanimod group, at a two-sided significance level of 0.05%.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 199 patients were randomly assigned to the trial groups, of whom 197 received placebo or ozanimod (Fig. S2 in the Supplementary Appendix). One patient in the placebo group and one in the group assigned to receive 0.5 mg of ozanimod did not receive the assigned regimen and were excluded from the analysis. The disease characteristics at baseline were similar among the three groups (Table 1). A total of 186 of the 197 patients (94%) completed the induction period. At week 8, a total of 103 patients who were considered by the investigators to have had clinical improvement (of whom 95 met the criteria for clinical response) continued in the blinded maintenance phase. Five patients who had a clinical response did not enter the maintenance phase (Table S7 in the Supplementary Appendix). A total of 91 of the 103 patients who entered the maintenance phase (88%) completed the trial.

EFFICACY

Primary Outcome

At week 8, clinical remission occurred in 11 of 67 patients (16%) who received 1 mg of ozanimod and in 9 of 65 patients (14%) who received 0.5 mg of ozanimod, as compared with 4 of 65 (6%) who received placebo (P=0.048 and P=0.14, respectively, for the comparison of the two doses of ozanimod with placebo) (Fig. 1A). No important differences were observed in subgroup analyses that were based on demographic characteristics and disease characteristics at baseline (Fig. S3 in the Supplementary Appendix).

Exploratory Outcomes

Given the nonsignificant findings for the comparison of the remission rate at week 8 in the group that received 0.5 mg of ozanimod with that in the placebo group, all subsequent analyses were considered to be exploratory and the results not significant (nominal P values are provided). Clinical response at week 8 occurred in 24 of 65 patients (37%) in the placebo group, as compared with 35 of 65 (54%) who received 0.5 mg of ozanimod (P=0.06) and 38 of 67 (57%) who received 1 mg of ozanimod (P=0.02) (Fig. 1B). Mucosal healing at week 8 occurred in 8 of 65 patients (12%) in the placebo group, as compared with 18 of 65 (28%) in the group that received 0.5 mg of ozanimod (P=0.03) and 23 of 67 (34%) in the group that received 1 mg of ozanimod (P=0.002) (Fig. 1C). Histologic remission, defined as a Geboes score of less than 2, at week 8 occurred in 7 of 65 patients (11%) in the placebo group, as compared with 9 of 65

Table 1. Demographic Characteristics and Disease Characteristics at Baseline, According to Trial Group.*

Characteristic	Placebo (N=65)	Ozanimod, 0.5 mg (N=65)	Ozanimod, 1 mg (N=67)
Male sex — no. (%)	35 (54)	32 (49)	48 (72)
Age — yr	41.9±12.3	38.8±12.1	41.8±11.0
White race — no. (%)†	61 (94)	59 (91)	62 (93)
Body weight — kg	72.6±14.9	72.3±16.9	77.4±16.3
Current smoker — no. (%)	3 (5)	4 (6)	4 (6)
Age at diagnosis — yr	35.8±13.0	33.1 ±11.3	35.2±12.1
Time since diagnosis — yr	6.1±5.5	5.9±5.4	6.7±6.8
Mayo Clinic score‡	8.6 ±1.5	8.3±1.5	8.5±1.6
Partial Mayo Clinic score‡	6.1±1.3	5.8±1.3	6.0±1.3
C-reactive protein — mg/liter			
Median	4.9	3.9	4.3
Range	0.20–141.4	0.10–131.2	0.10–82.5
Fecal calprotectin — μg/g			
Median	1272	1477	1238
Range	30–8380	66–11,108	10–10,511
Lactoferrin — μg/g			
Median	29.0	30.6	29.9
Range	1.4–1049	1.4–483	1.4–586
Hemoglobin — g/liter	123.7±20.1	119.7±20.5	126.0±20.7
Extent of disease — no. (%)			
Left side of colon	41 (63)	41 (63)	41 (61)
Extensive	24 (37)	24 (37)	26 (39)
Concomitant medication use — no. (%)			
Glucocorticoid	24 (37)	22 (34)	27 (40)
Aminosalicylate	57 (88)	53 (82)	53 (79)
Previous medication use — no. (%)			
Immunosuppressive agent§	17 (26)	24 (37)	22 (33)
TNF-antagonist therapy	10 (15)	13 (20)	13 (19)

* Plus–minus values are means ±SD. There were no significant differences among the three groups in any of the baseline characteristics. Normal values are as follows: C-reactive protein, less than 5 mg per liter; fecal calprotectin, less than 50 μg per gram of stool; lactoferrin, 6.0 μg or less per gram of stool; and hemoglobin, 125 to 170 g per liter in men and 110 to 155 g per liter in women. TNF denotes tumor necrosis factor.

† Race was self-reported.

‡ The Mayo Clinic score was used to measure disease activity; scores range from 0 to 12, with higher values indicating more severe disease. The partial Mayo Clinic score consists of the Mayo Clinic score minus the sigmoidoscopy subscore; the partial score ranges from 0 to 9, with higher scores indicating more active disease.

§ Immunosuppressive agents included azathioprine, methotrexate, and mercaptopurine.

(14%) in the group that received 0.5 mg of ozanimod (P=0.63) and 15 of 67 (22%) in the group that received 1 mg of ozanimod (P=0.07) (Fig. 1D).

Absolute lymphocyte counts in blood decreased by a mean of 32% from baseline to week 8 in patients who received 0.5 mg of ozanimod and by 49% in patients who received 1 mg of ozanimod. At week 8, a total of 30% of the patients in the group that received 0.5 mg of ozanimod and 53% of those in the group that received 1 mg of ozanimod had absolute lymphocyte counts

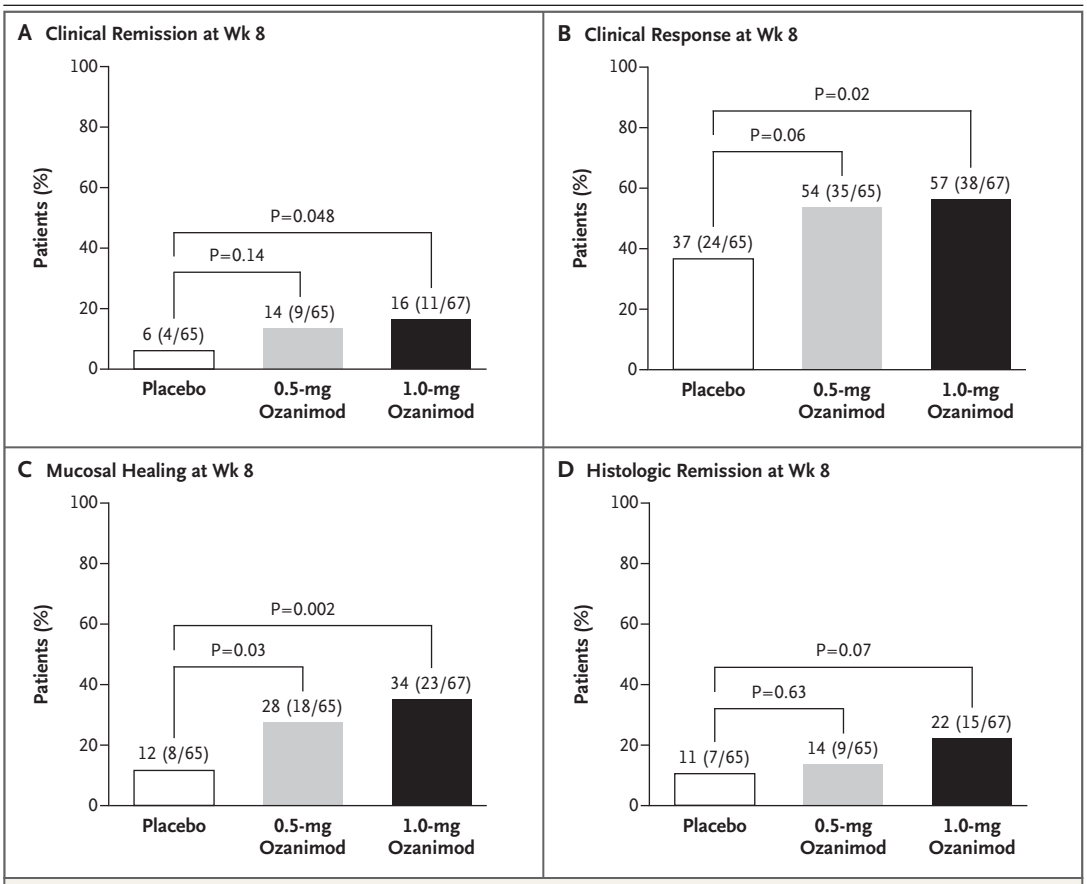

Figure 1. Efficacy Outcomes at Week 8 in the Trial of Ozanimod as Induction Therapy.

Panel A shows the percentage of patients in the three trial groups who had a clinical remission (Mayo Clinic score ≤2, with no individual subscore >1) at week 8 (the primary outcome). Mayo Clinic scores range from 0 to 12, with higher values indicating more severe disease; subscores range from 0 to 3, with higher scores indicating more severe disease. Panel B shows the percentage of patients who had a clinical response (defined as a reduction from baseline in the Mayo Clinic score of ≥3 points and ≥30%, and a decrease from baseline in the rectal-bleeding subscore of ≥1 point or an absolute rectal-bleeding subscore of ≤1 point) at week 8. Panel C shows the percentage of patients with mucosal healing (endoscopy subscore of ≤1 point) at week 8. Panel D shows the percentage of patients with histologic remission (Geboes score <2, on a scale from 0 to 5, with higher scores indicating more severe histologic inflammation) at week 8. P values reported for analyses other than the primary outcome of clinical remission at week 8 are considered to be nominal and not significant.

that were below the lower limit of the normal range, with the majority of patients in each ozanimod group having grade 1 or grade 2 reductions in the lymphocyte count. A total of 9 of 67 patients in the group that received 1 mg of ozanimod had grade 3 reductions in the lymphocyte count, and no patient in either ozanimod group had grade 4 lymphopenia (Table S6 in the Supplementary Appendix).

Figure 2 shows the proportions of patients with clinical remission, clinical response, mucosal healing, and histologic remission at week 32. A total of 2 of 4 patients with remission at week 8 in the placebo group, 7 of 9 in the group that received 0.5 mg of ozanimod, and 5 of 11 in the group that received 1 mg of ozanimod still had remission at week 32. Reductions in the Mayo Clinic score and in the serum and fecal inflammatory laboratory variables (C-reactive protein, calprotectin, and lactoferrin concentrations) were consistent with the higher degree of efficacy seen in the group that received 1 mg of ozanimod (Table S12 in the Supplementary Appendix). These data should be interpreted cautiously given that the usefulness of these markers is highly dependent on clinical context.[22]

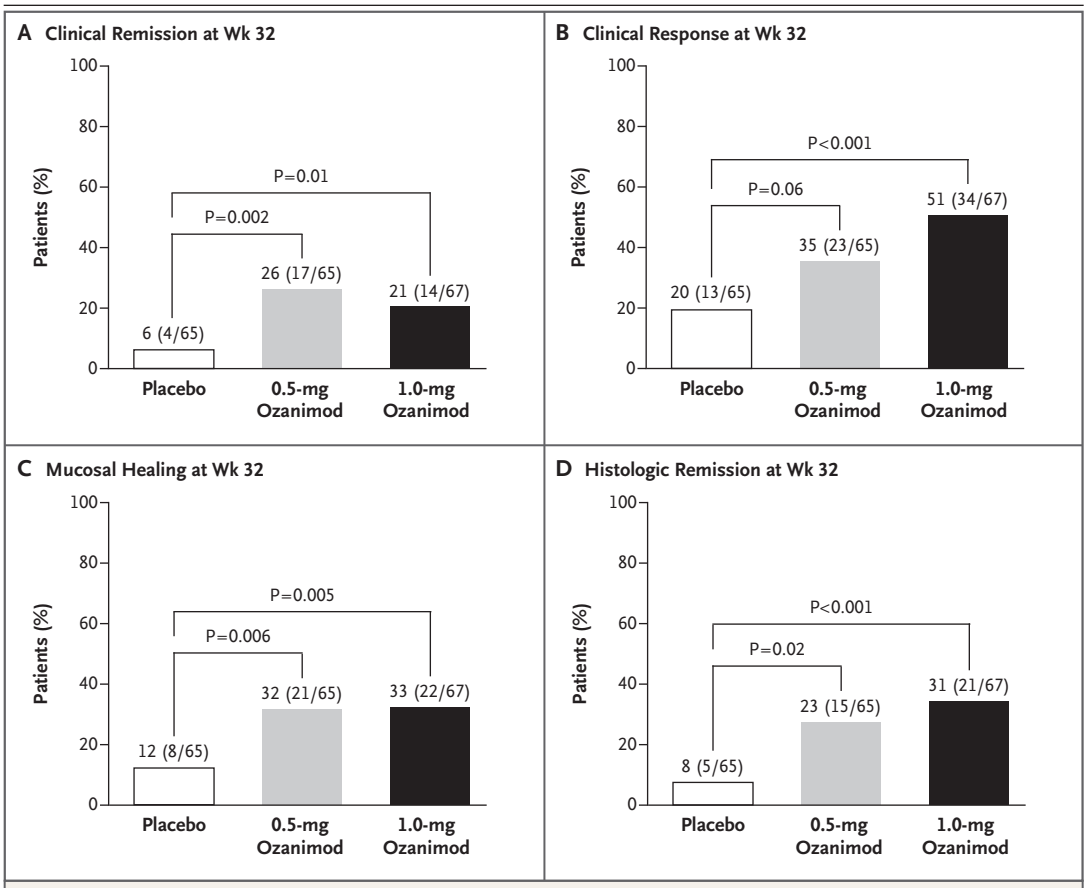

Figure 2. Exploratory Efficacy Outcomes at Week 32 in the Trial of Ozanimod as Maintenance Therapy.
The P values reported for these analyses are considered to be nominal and not significant.

SAFETY

No important differences were observed among the groups in the most commonly reported adverse events during the trial (Table 2). One patient in the 0.5-mg ozanimod group who had evidence of preexisting bradycardia (heart rate of 50 beats per minute and a PR interval of 198 msec before ozanimod treatment was initiated) had first-degree atrioventricular block and sinus bradycardia on day 8 (heart rate, 46 beats per minute; PR interval, 201 msec [upper limit of the normal range, 200 msec]); this event was asymptomatic and transient and resolved without intervention. The patient discontinued treatment after these events. Four patients who received ozanimod (one patient who received 0.5 mg and three who received 1 mg) had an increase in the alanine aminotransferase level of more than 3 times the upper limit of the normal range during treatment. Squamous-cell carcinoma of the skin developed in one patient who received 1 mg of ozanimod; this patient had previously been treated with mercaptopurine for more than 2 years.

DISCUSSION

In this phase 2 trial involving patients with moderately or severely active ulcerative colitis, treatment with ozanimod at a once-daily oral dose of 1 mg resulted in slightly higher rates of clinical remission at week 8 than those with placebo (16% vs. 6%, P=0.048). At week 32, patients receiving 1 mg of ozanimod continued to have higher rates of clinical remission, clinical response, mucosal healing, and histologic remission, as well as lower Mayo Clinic scores, than those with placebo. The increases in the proportions of patients with clinical remission and with histologic remission at week 32, as compared with week 8, raise the possibility that

Table 2. Safety Findings in Induction and Maintenance Phases, According to Trial Group.

Event	Placebo (N=65)	Ozanimod, 0.5 mg (N=65)	Ozanimod, 1 mg (N=67)
No. of adverse events	59	45	51
Adverse event — no. of patients (%)	26 (40)	26 (40)	26 (39)
Serious adverse event — no. of patients (%)*	6 (9)	1 (2)	3 (4)
Adverse event leading to discontinuation of regimen — no. of patients (%)	4 (6)	3 (5)	1 (1)
Adverse cardiac event — no. of patients (%)	2 (3)	1 (2)	0
Adverse event occurring in ≥2 patients receiving ozanimod — no. of patients (%)			
Ulcerative colitis flare	5 (8)	2 (3)	3 (4)
Anemia	4 (6)	3 (5)	0
Headache	3 (5)	0	2 (3)
Nausea	2 (3)	1 (2)	2 (3)
Pyrexia	0	1 (2)	3 (4)
Arthralgia	1 (2)	1 (2)	2 (3)
Alanine aminotransferase increased	0	1 (2)	3 (4)
Back pain	1 (2)	1 (2)	1 (1)
Rash	0	1 (2)	2 (3)
Abdominal pain	1 (2)	1 (2)	1 (1)
Vomiting	0	0	2 (3)
Orthostatic hypotension	0	2 (3)	0
Aspartate aminotransferase increased	0	1 (2)	1 (1)
Hyperbilirubinemia	0	1 (2)	1 (1)
Insomnia	0	1 (2)	1 (1)
Nasopharyngitis	0	2 (3)	0
Proctalgia	0	1 (2)	1 (1)

* A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening (was associated with an immediate risk of death), required admission to a hospital or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, or resulted in a congenital anomaly or birth defect. Events occurring in the placebo group included worsening ulcerative colitis in three patients, iron-deficiency anemia in one, herpes zoster infection and autoimmune hemolytic anemia in one, and jaundice in one. One patient in the group that received 0.5 mg of ozanimod had hyperpyrexia. Events occurring in the group that received 1.0 mg of ozanimod included worsening ulcerative colitis in two patients and adenoma of the colon in one.

extended treatment may be associated with enhanced efficacy.

Studies of other agents, notably monoclonal antibodies directed toward adhesion molecules, have previously shown that interference with lymphocyte trafficking is an effective therapeutic approach for patients with ulcerative colitis. The use of orally administered small molecules as alternatives to injectable monoclonal antibodies for the treatment of ulcerative colitis has both advantages and disadvantages. With respect to the advantages, the convenience of oral administration is attractive to patients and providers. Even more important, avoidance of sensitization with the formation of antidrug antibodies has the potential to eliminate one of the most important reasons for the failure of treatment with monoclonal antibodies. Alternatively, small molecules can be less selective than monoclonal antibodies, and off-target binding may result in adverse effects.

This trial was not large enough or of sufficiently long duration to assess the safety of ozanimod. As noted previously, S1P-receptor

modulators have been associated with cardiac and hepatic effects.[15] Elevations in hepatic aminotransferase levels were observed in four patients (3%) receiving ozanimod and require further evaluation. First-degree atrioventricular block and sinus bradycardia developed on day 8 in one patient who was treated with ozanimod. Patients with clinically significant cardiovascular disease, including those with bradycardia and those taking medications that affect the cardiac conduction system, were excluded from the trial, so our findings cannot be extrapolated to these patient populations.

Our trial had some limitations. First, the time point of week 8 that was chosen for the evaluation of efficacy during induction may not be long enough for drugs that target lymphocyte trafficking, a possibility that is supported by the enhanced benefits seen in maintenance with antitrafficking agents.[2] Second, as noted above, given the relatively brief duration of observation and the small number of patients evaluated, we cannot assess the safety of ozanimod. Third, ozanimod treatment resulted in large reductions from baseline in absolute lymphocyte counts, with most patients in the group that received 1 mg having counts below the lower limit of the normal range at week 8 — a finding that is consistent with the mechanism of the drug. Future studies are needed to assess the risk of infections associated with ozanimod. Finally, the trial was limited to patients receiving ozanimod as monotherapy or in combination with glucocorticoids or aminosalicylates.

In conclusion, in this preliminary trial, ozanimod at a dose of 1 mg was associated with a slightly higher rate of clinical remission among patients with moderately to severely active ulcerative colitis than the rate with placebo. Efficacy requires further assessment in larger trials. This trial was not large enough or of sufficiently long duration to assess safety.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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